BRETYLIUM & GUANETHIDINE

Two New Drugs Producing Specific Blockade of the Sympathetic Nervous System

EDWARD D. FREIS, M.D.

Senior Medical Investigator, Veterans Administration Hospital, Washington, D.C.

The purpose of this communication is to acquaint practicing physicians with a new class of antihypertensive agents. The ganglion blocking drugs are recognized as the most potent and reliable antihypertensive agents presently available. In clinical practice, however, their use is attended by a high incidence of side effects. Ganglioplegic drugs inhibit transmission through all autonomic ganglia, parasympathetic as well as sympathetic. Such side effects of parasympathetic blockade as paralysis of visual accommodation, dryness of the mouth, and constipation have contributed to the discomforts patients frequently experience with these agents. Since, as far as is known, the antihypertensive effects of these drugs result entirely from blockade of the sympathetic and not at all from blockade of the parasympathetic system, new agents have been sought which would block transmission only through sympathetic nerves.

As often happens, two such drugs have been discovered practically simultaneously, one in England, the other in this country. The British compound is bretylium tosylate (Darenthin®). The American drug is guanethidine (Ismelin®). Both agents seem to block transmission at or near the sympathetic nerve endings. They do not block at the ganglia and they apparently have no inhibiting effect on parasympathetic transmission. Unlike the adrenergic blocking agents such as tolazoline and phentolamine, they do not neutralize or reverse the pressor effects of circulating epinephrine and norepinephrine. They represent, in truth, a new class of compounds whose blocking effects seem to be limited to transmission of sympathetic nerve impulses.

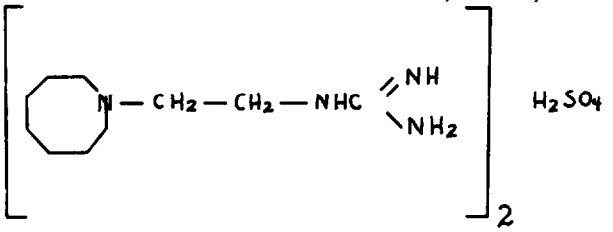
guanethidine

The pharmacology of guanethidine was described in 1959. Maxwell and associates found that the drug lowered blood pressure in hypertensive animals, blocked transmission through postganglionic sympathetic but not parasympathetic nerves, and did not prevent the pressor effects of injected norepinephrine. In addition, they reported an unusually long duration of action. The effects of a large, single dose were found to last for one week or longer.

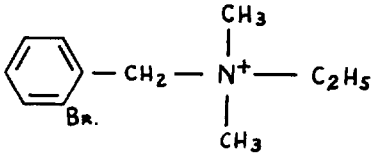
Clinical trials in several clinics quickly confirmed the fact that guanethidine was a potent antihypertensive agent in doses of 25 to 200 mg. per day, depending on the responsiveness of the patient. Postural hypotension resulted, although blood pressure was reduced to a lesser degree in the supine position as well, similar to effects of the ganglion blocking drugs; however, unlike the latter, side effects of constipation, loss of visual accommodation, dry mouth, and difficulty in emptying the urinary bladder were entirely absent. Indeed, diarrhea, which may be caused by unopposed parasympathetic activity, has been a common side effect. Bradycardia has been another evidence of parasympathetic predominance. Libido and erection are not affected although ejaculation which is a sympathetic function may not be consummated.

The long duration of action of guanethidine has necessitated certain precautions in adjusting dosages. Since the duration of action spans a period of approximately one week the daily dosages given during that period will, to a certain extent, be cumulative. Therefore, in ambulatory patients it has been found to be

Chemical Structure of Guanethidine and Bretylium Tosylate



[2-(octahydro-1-azocinyl)-ethyl] guanidine sulfate, guanethidine.



N-O-bromobenzyl-N-ethyl-NN-dimethylammonium ion, bretylium.

prudent to wait at least one week before elevating the dose level. When dosages were raised more rapidly orthostatic hypotension and collapse could be precipitated, and sometimes they lasted for four or five days after the drug was withdrawn. This, of course, is a more important problem in ambulatory than in hospitalized patients. In the former, dosage increases should be planned so as gradually to approach a therapeutic maintenance level, at which daily destruction and excretion equal the daily intake.

bretylium tosylate

At about the same time that findings with guanethidine were announced a group of British investigators published their report that bretylium tosylate, a compound which is chemically wholly different from guanethidine, also produced selective block of the sympathetic nervous system. Administration of the isotopically labeled compound showed that it was incorporated into sympathetic nerves in higher concentration than in other nervous tissue.

Clinical trials of bretylium first in England and then in this country indicated that the drug produced predominantly a postural hypotension and that it was free of the side effects of parasympathetic blockade. It was poorly absorbed from the gastrointestinal tract so that large doses, sometimes exceeding 300 mg. per day, were required. Unlike guanethidine, the duration of action of the drug was approximately eight to twelve hours, so that dosages could be administered every eight hours and elevated fairly rapidly to the effective level without danger of precipitating a prolonged hypotensive episode. Also, unlike guanethidine, the side effects of parasympathetic predominance—diarrhea and bradycardia—did not occur.

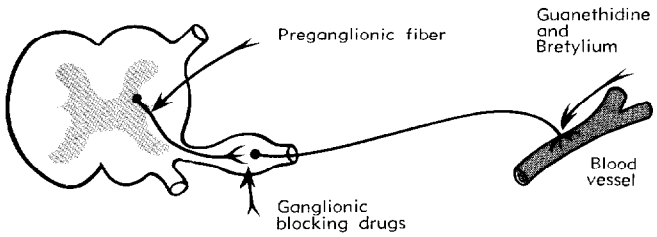
Among the principal shortcomings of bretylium are: (1) an unusually wide range of dose responses (from 300 to over 3000 mg. per day in divided dosage) in different patients; (2) lack of antihypertensive potency in more severe and resistant cases; and (3) development of tolerance in some patients. A side effect peculiar to this drug has been the development of bilateral pain and tenderness but without swelling, heat, or redness in the region of the parotid gland. The cause is unknown and it most often occurs when dosages are elevated to levels of two or more grams per day.

general comments

The antihypertensive effect of both of these agents is primarily orthostatic. In this respect they are similar to the ganglion blocking agents in that the blood pressure in the supine position is the least affected by the drug. The only advantage of guanethidine and bretylium is the absence of parasympathetic blocking effects. Because of the effect of blocking agents of either type on orthostatic blood pressure meticulous dosage adjustment is required in order to avoid postural collapse. With ambulatory patients, in my experience, the best guide is frequent home blood pressure recordings taken when the patient is standing in the erect position. Unfortunately, guanethidine and bretylium do not do away with the necessity for such precautions. Just as chlorothiazide and other saluretic agents have enhanced the effectiveness of the ganglion blocking drugs so have they also been used to advantage with bretylium and guanethidine.

It is still too early to say how important a place these agents will have in the clinical management of patients with hypertension or to be detailed and specific about the most effective means for administering these drugs. Probably they represent promising forerunners of better agents to come which will combine the potency of the ganglion blocking drugs without their parasympathetic blocking effects.

Action Sites: Ganglion Blocking Agents, Guanethidine & Bretylium



Ganglion blocking agents inhibit transmission through autonomic ganglia (sympathetic and parasympathetic), guanethidine and bretylium at or near endings of postganglionic sympathetic fibers.

references

Boura, A. L. A., et al.: Darenthin: Hypotensive Agent of a New Type, Lancet 2:17 (July 11) 1959.

Dollery, C. T., et al.: Bretylium Tosylate in the Treatment of Hypertension, Lancet 1:296 (Feb. 6) 1960.

Frohlich, E. D., and Freis, E. D.: Clinical Trial of Guanethidine, a New Type of Antihypertensive Agent, M. Ann. District of Columbia 28:419 (Aug.) 1959.

Maxwell, R. A., et al.: Pharmacology of [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate (SU-5864), J. Pharmacol. & Exper. Therap. 128:22 (Jan.) 1960.

Page, I. H., and Dustan, H. P.: A New Potent Antihypertensive Drug. Preliminary Study of [2-(octahydro-1-azocinyl)-ethyl]-guanidine Sulfate (Guanethidine), J. Am. M. A. 170:1265 (July 11) 1959.

Richardson, D. W. and Wyso, E. M.: Effective Reduction in Blood Pressure without Ganglionic Blockade, Virginia M. Month. 86:377 (July) 1959.